

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074400

Trade Name : DIFLUNISAL TABLETS USP

Generic Name: Diflunisal Tablets USP, 250mg and 500mg

Sponsor : Danbury Pharmacal, Inc.

Approval Date: July 17, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION **074400**

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology				
Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074400

APPROVAL LETTER

JUL 17 1997

Danbury Pharmacal, Inc.
Attention: William R. McIntyre, Ph.D.
131 West Street
Danbury, CT 06810

Dear Sir:

This is in reference to your abbreviated new drug application dated August 5, 1993, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Diflunisal Tablets USP, 250 mg and 500 mg.

Reference is also made to your amendments dated February 17 and April 14, 1994, April 30, November 20, 1996 and June 27, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your 250 and 500 mg tablets to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Dolobid Tablets 250 mg and 500 mg, respectively, of Merck and Co., Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign, at the time of their initial use, be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253.

Sincerely yours,

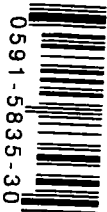
7-17-97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER **074400**

FINAL PRINTED LABELING



0591-5835-30

Each tablet contains:
Diflunisal, USP 250 mg
Store at controlled room temperature,
15°-30°C (59°-86°F).

DANBURY
PHARMACAL, INC.

NDC 0591-5835-30

**DIFLUNISAL
TABLETS, USP**

250 mg

CAUTION: Federal law prohibits
dispensing without prescription.

30 TABLETS

USUAL DOSAGE: See package insert for
dosage and full prescribing information.
Dispense in a well-closed container
with a child-resistant closure.

Control No. and Exp. Date
LABEL
SAMPLE



0591-5835-08

Each tablet contains:
Diflunisal, USP 250 mg
Store at controlled room temperature,
15°-30°C (59°-86°F).

DANBURY
PHARMACAL, INC.

NDC 0591-5835-08

**DIFLUNISAL
TABLETS, USP**

250 mg

CAUTION: Federal law prohibits
dispensing without prescription.

60 TABLETS

USUAL DOSAGE: See package insert for
dosage and full prescribing information.
Dispense in a well-closed container
with a child-resistant closure.

Control No. and Exp. Date
LABEL
SAMPLE



N 0591-5835-03 8

Each tablet contains:
Diflunisal, USP 250 mg
Store at controlled room temperature,
15°-30°C (59°-86°F).

DANBURY
PHARMACAL, INC.
DANBURY, CT 06810

NDC 0591-5835-03

**DIFLUNISAL
TABLETS, USP**

250 mg

CAUTION: Federal law prohibits
dispensing without prescription.

500 TABLETS

USUAL DOSAGE: See package insert for
dosage and full prescribing information.
Dispense in a well-closed container with a
child-resistant closure.

Control No. and Exp. Date
LABEL
SAMPLE



N 0591-5835-04 5

Each tablet contains:
Diflunisal, USP 250 mg
Store at controlled room temperature,
15°-30°C (59°-86°F).

DANBURY
PHARMACAL, INC.
DANBURY, CT 06810

NDC 0591-5835-04

**DIFLUNISAL
TABLETS, USP**

250 mg

CAUTION: Federal law prohibits
dispensing without prescription.

1000 TABLETS

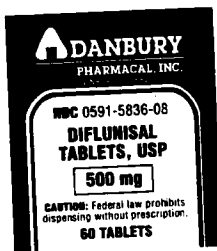
USUAL DOSAGE: See package insert for
dosage and full prescribing information.
Dispense in a well-closed container with a
child-resistant closure.

Control No. and Exp. Date
LABEL
SAMPLE



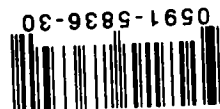
0591-5836-08

Each tablet contains:
Diflunisal, USP 500 mg
Store at controlled room temperature,
15°-30°C (59°-86°F).



USUAL DOSAGE: See package insert for dosage and full prescribing information. Dispense in a well-closed container with a child-resistant closure.

Control No. and Exp. Date
LABEL
SAMPLE

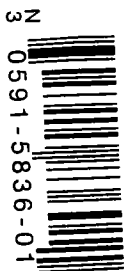


0591-5836-30
Store at controlled room temperature,
15°-30°C (59°-86°F).
Diflunisal, USP 500 mg



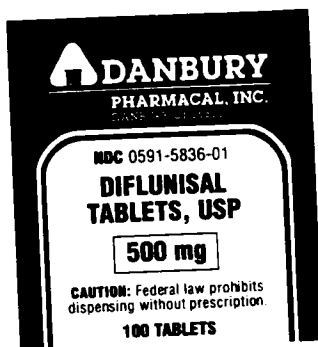
USUAL DOSAGE: See package insert for dosage and full prescribing information. Dispense in a well-closed container with a child-resistant closure.

Control No. and Exp. Date
LABEL
SAMPLE



N 0591-5836-01 1

Each tablet contains:
Diflunisal, USP 500 mg
Store at controlled room temperature,
15°-30°C (59°-86°F).



USUAL DOSAGE: See package insert for dosage and full prescribing information. Dispense in a well-closed container with a child-resistant closure.

Control No. and Exp. Date
LABEL
SAMPLE



N 0591-5836-03 5

Each tablet contains:
Diflunisal, USP 500 mg
Store at controlled room temperature,
15°-30°C (59°-86°F).



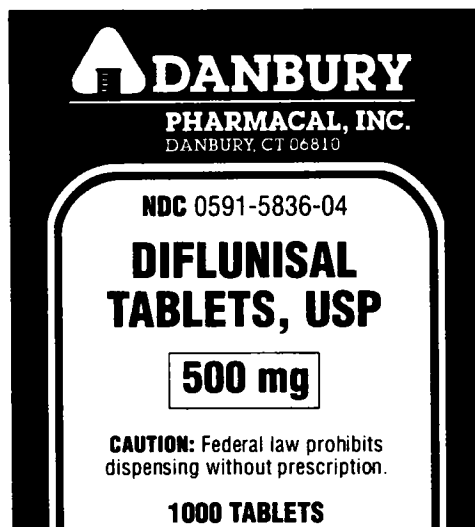
USUAL DOSAGE: See package insert for dosage and full prescribing information. Dispense in a well-closed container with a child-resistant closure.

Control No. and Exp. Date
LABEL
SAMPLE



N 0591-5836-04 2

Each tablet contains:
Diflunisal, USP 500 mg
Store at controlled room temperature,
15°-30°C (59°-86°F).



USUAL DOSAGE: See package insert for dosage and full prescribing information. Dispense in a well-closed container with a child-resistant closure.

Control No. and Exp. Date
LABEL
SAMPLE



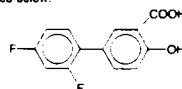
DIFLUNISAL Tablets, USP

Revised: October 1996

JUL 17 1997

DESCRIPTION

Diflunisal is 2', 4'-difluoro-4-hydroxy-3-biphenyl-carboxylic acid. It is a stable, white, crystalline compound with a melting point of 211-213°C. It is practically insoluble in water at neutral or acidic pH. Because it is an organic acid, it dissolves readily in dilute alkali to give a moderately stable solution at room temperature. It is soluble in most organic solvents including ethanol, methanol, and acetone. The structural formula is represented below:



$C_{13}H_8F_2O_3$

M.W. 250.20

Each tablet, for oral administration, contains diflunisal 250 mg or 500 mg.

Diflunisal Tablets, USP 250 mg and 500 mg contain the following inactive ingredients: colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, pregelatinized starch, sodium starch glycolate, starch, talc and titanium dioxide.

CLINICAL PHARMACOLOGY

Action

Diflunisal is a non-steroidal drug with analgesic, anti-inflammatory and antipyretic properties. It is a peripherally-acting non-narcotic analgesic drug. Habituation, tolerance and addiction have not been reported.

Diflunisal is a difluorophenyl derivative of salicylic acid. Chemically, diflunisal differs from aspirin (acetylsalicylic acid) in two respects. The first of these two is the presence of a difluorophenyl substituent at carbon 1. The second difference is the removal of the O-acetyl group from the carbon 4 position. Diflunisal is not metabolized to salicylic acid, and the fluorine atoms are not displaced from the difluorophenyl ring structure.

The precise mechanism of the analgesic and anti-inflammatory actions of diflunisal is not known. Diflunisal is a prostaglandin synthetase inhibitor. In animals, prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain. Since prostaglandins are known to be among the mediators of pain and inflammation, the mode of action of diflunisal may be due to a decrease of prostaglandins in peripheral tissues.

Pharmacokinetics and Metabolism

Diflunisal is rapidly and completely absorbed following oral administration with peak plasma concentrations occurring between 2 to 3 hours. The drug is excreted in the urine as two soluble glucuronide conjugates accounting for about 90% of the administered dose. Little or no diflunisal is excreted in the feces. Diflunisal appears in human milk in concentrations of 2-7% of those in plasma. More than 99% of diflunisal in plasma is bound to proteins.

As is the case with salicylic acid, concentration-dependent pharmacokinetics prevail when diflunisal is administered; a doubling of dosage produces a greater than doubling of drug accumulation. The effect becomes more apparent with repetitive doses. Following single doses, peak plasma concentrations of $41 \pm 11 \mu\text{g/mL}$ (mean \pm S.D.) were observed following 250 mg doses, $87 \pm 17 \mu\text{g/mL}$ were observed following 500 mg and $124 \pm 11 \mu\text{g/mL}$ following single 1000 mg doses. However, following administration of 250 mg b.i.d., a mean peak level of $56 \pm 14 \mu\text{g/mL}$ was observed on day 8, while the mean peak level after 500 mg b.i.d. for 11 days was $190 \pm 33 \mu\text{g/mL}$. In contrast to salicylic acid which has a plasma half-life of 2-4 hours, the plasma half-life of diflunisal is 3 to 4 times longer (8 to 12 hours), because of a difluorophenyl substituent at carbon 1. Because of its long half-life and nonlinear pharmacokinetics, several days are required for diflunisal plasma levels to reach steady state following multiple doses. For this reason, an initial loading dose is necessary to shorten the time to reach steady state levels, and 2 to 3 days of observation are necessary for evaluating changes in treatment regimens if a loading dose is not used.

Studies in baboons to determine passage across the blood-brain barrier have shown that only small quantities of diflunisal under normal or acidic

2

Diffunisal is a non-steroidal anti-inflammatory drug (NSAID) with a long half-life. The effect becomes more apparent with repetitive doses. Following single doses, peak plasma concentrations of $41 \pm 11 \mu\text{g/mL}$ (mean \pm S.D.) were observed following 250 mg doses. $87 \pm 17 \mu\text{g/mL}$ were observed following 500 mg and $124 \pm 11 \mu\text{g/mL}$ following single 1000 mg doses. However, following administration of 250 mg b.i.d., a mean peak level of $56 \pm 14 \mu\text{g/mL}$ was observed on day 8, while the mean peak level after 500 mg b.i.d. for 11 days was $190 \pm 33 \mu\text{g/mL}$. In contrast to salicylic acid which has a plasma half-life of 2 1/4 hours, the plasma half-life of diflunisal is 3 to 4 times longer (8 to 12 hours), because of a difluorophenyl substituent at carbon 1. Because of its long half-life and nonlinear pharmacokinetics, several days are required for diflunisal plasma levels to reach steady state following multiple doses. For this reason, an initial loading dose is necessary to shorten the time to reach steady state levels, and 2 to 3 days of observation are necessary for evaluating changes in treatment regimens if a loading dose is not used.

Studies in baboons to determine passage across the blood-brain barrier have shown that only small quantities of diflunisal, under normal or acidic conditions are transported into the cerebrospinal fluid (CSF). The ratio of blood/CSF concentrations after intravenous doses of 50 mg/kg or oral doses of 100 mg/kg of diflunisal was 100:1. In contrast, oral doses of 500 mg/kg of aspirin resulted in a blood/CSF ratio of 5:1.

Used to Moderate Pain

Diflunisal is a peripherally-acting analgesic agent with a long duration of action. Diflunisal produces significant analgesia within 1 hour and maximum analgesia within 2 to 3 hours.

Consistent with its long half-life, clinical effects of diflunisal mirror its pharmacokinetic behavior, which is the basis for recommending a loading dose when instituting therapy. Patients treated with diflunisal, on the first dose, tend to have a slower onset of pain relief when compared with drugs achieving comparable peak effects. However, diflunisal produces longer-lasting responses than the comparative agents.

Comparative single dose clinical studies have established the analgesic efficacy of diflunisal at various dose levels relative to other analgesics. Analgesic effect measurements were derived from hourly evaluations by patients during eight and twelve-hour postdosing observation periods. The following information may serve as a guide for prescribing diflunisal.

Diflunisal 500 mg was comparable in analgesic efficacy to aspirin 650 mg, acetaminophen 600 mg or 650 mg, and acetaminophen 650 mg with propoxyphene napsylate 100 mg. Patients treated with diflunisal had longer lasting responses than the patients treated with the comparative analgesics.

Diflunisal 1000 mg was comparable in analgesic efficacy to acetaminophen 600 mg with codeine 60 mg. Patients treated with diflunisal had longer lasting responses than the patients who received acetaminophen with codeine.

A loading dose of 1000 mg provides faster onset of pain relief, shorter time to peak analgesic effect, and greater peak analgesic effect than an initial 500 mg dose.

In contrast to the comparative analgesics, a significantly greater proportion of patients treated with diflunisal did not remedicate and continued to have a good analgesic effect eight to twelve hours after dosing. Seventy-five percent (75%) of patients treated with diflunisal continued to have a good analgesic response at four hours. When patients having a good analgesic response at four hours were followed, 78% of these patients continued to have a good analgesic response at eight hours and 64% at twelve hours.

Chronic Anti-Inflammatory Therapy in Osteoarthritis and Rheumatoid Arthritis

In the controlled, double-blind clinical trials in which diflunisal (500 mg to 1000 mg a day) was compared with anti-inflammatory doses of aspirin (2-4 grams a day), patients treated with diflunisal had a significantly lower incidence of tinnitus and of adverse effects involving the gastrointestinal system than patients treated with aspirin. (See also **Effect on Fecal Blood Loss**).

Osteoarthritis

The effectiveness of diflunisal for the treatment of osteoarthritis was studied in patients with osteoarthritis of the hip and/or knee. The activity of diflunisal was demonstrated by clinical improvement in the signs and symptoms of disease activity.

In a double-blind multicenter study of 12 weeks' duration in which dosages were adjusted according to patient response, diflunisal 500 or 750 mg daily was shown to be comparable in effectiveness to aspirin, 2000 or 3000 mg daily. In open-label extensions of this study to 24 or 48 weeks, diflunisal continued to show similar effectiveness and generally was well tolerated.

Rheumatoid Arthritis

In controlled clinical trials, the effectiveness of diflunisal was established for both acute exacerbations and long-term management of rheumatoid arthritis. The activity of diflunisal was demonstrated by clinical improvement in the signs and symptoms of disease activity.

In a double-blind multicenter study of 12 weeks' duration in which dosages were adjusted according to patient response, diflunisal 500 or 750 mg daily was comparable in effectiveness to aspirin 2600 mg or 3900 mg daily. In open-label extensions of this study to 52 weeks, diflunisal continued to be effective and was generally well tolerated.

Diflunisal 500, 750, or 1000 mg daily was compared with aspirin 2000, 3000, or 4000 mg daily in a multicenter study of 8 weeks' duration in which dosages were adjusted according to patient response. In this study, diflunisal was comparable in efficacy to aspirin.

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3

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In a double-blind multicenter study of 12 weeks' duration in which dosages were adjusted according to patient needs, diflunisal 500 or 750 mg daily and ibuprofen 1600 or 2400 mg daily were comparable in effectiveness and tolerability.

In a double-blind multicenter study of 12 weeks' duration, diflunisal 750 mg daily was comparable in efficacy to naproxen 750 mg daily. The incidence of gastrointestinal adverse effects and tinnitus was comparable for both drugs. This study was extended to 48 weeks on an open-label basis. Diflunisal continued to be effective and generally well tolerated.

In patients with rheumatoid arthritis, diflunisal and gold salts may be used in combination at their usual dosage levels. In clinical studies, diflunisal added to the regimen of gold salts usually resulted in additional symptomatic relief but did not alter the course of the underlying disease.

Antipyretic Activity

Diflunisal is not recommended for use as an antipyretic agent. In single 250 mg, 500 mg, or 750 mg doses, diflunisal produced measurable but not clinically useful decreases in temperature in patients with fever; however, the possibility that it may mask fever in some patients, particularly with chronic or high doses, should be considered.

Uricosuric Effect

In normal volunteers, an increase in the renal clearance of uric acid and a decrease in serum uric acid was observed when diflunisal was administered at 500 mg or 750 mg daily in divided doses. Patients on long-term therapy taking diflunisal at 500 mg to 1000 mg daily in divided doses showed a prompt and consistent reduction across studies in mean serum uric acid levels, which were lowered as much as 1.4 mg%. It is not known whether diflunisal interferes with the activity of other uricosuric agents.

Effect on Platelet Function

As an inhibitor of prostaglandin synthetase, diflunisal has a dose-related effect on platelet function and bleeding time. In normal volunteers, 250 mg b.i.d. for 8 days had no effect on platelet function, and 500 mg b.i.d., the usual recommended dose, had a slight effect. At 1000 mg b.i.d., which exceeds the maximum recommended dosage, however, diflunisal inhibited platelet function. In contrast to aspirin, these effects of diflunisal were reversible, because of the absence of the chemically labile and biologically reactive O-acetyl group at the carbon 4 position. Bleeding time was not altered by a dose of 250 mg b.i.d., and was only slightly increased at 500 mg b.i.d. At 1000 mg b.i.d., a greater increase occurred, but was not statistically significantly different from the change in the placebo group.

Effect on Fecal Blood Loss

When diflunisal was given to normal volunteers at the usual recommended dose of 500 mg twice daily, fecal blood loss was not significantly different from placebo. Aspirin at 1000 mg four times daily produced the expected increase in fecal blood loss. Diflunisal at 1000 mg twice daily (NOTE: exceeds the recommended dosage) caused a statistically significant increase in fecal blood loss, but this increase was only one-half as large as that associated with aspirin 1300 mg twice daily.

Effect on Blood Glucose

Diflunisal did not affect fasting blood sugar in diabetic patients who were receiving tolbutamide or placebo.

INDICATIONS AND USAGE

Diflunisal tablets are indicated for acute or long-term use for symptomatic treatment of the following:

1. Mild to moderate pain
2. Osteoarthritis
3. Rheumatoid arthritis

CONTRAINDICATIONS

Patients who are hypersensitive to this product. Patients in whom acute asthmatic attacks, urticaria, or rhinitis are precipitated by aspirin or other non-steroidal anti-inflammatory drugs.

WARNINGS

Peptic ulceration and gastrointestinal bleeding have been reported in patients receiving diflunisal. Fatalities have occurred rarely. Gastrointestinal bleeding is associated with higher morbidity and mortality in patients acutely ill with other conditions, the elderly and patients with hemorrhagic disorders. In patients with active gastrointestinal bleeding or an active peptic ulcer, the physician must weigh the benefits of therapy with diflunisal against possible hazards, institute an appropriate ulcer regimen, and carefully monitor the patient's progress. When diflunisal is given to patients with a history of either upper or lower gastrointestinal tract disease, it should be given only after consulting the ADVERSE REACTIONS section and under close supervision.

Risk of GI Ulcerations, Bleeding and Perforation with NSAID Therapy

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal prob-

Risk of GI Ulcerations, Bleeding and Perforation with NSAID Therapy

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS

General

Non-steroidal anti-inflammatory drugs, including diflunisal, may mask the usual signs and symptoms of infection. Therefore, the physician must be continually on the alert for this and should use the drug with extra care in the presence of existing infection.

Although diflunisal has less effect on platelet function and bleeding time than aspirin, at higher doses it is an inhibitor of platelet function; therefore, patients who may be adversely affected should be carefully observed when diflunisal is administered (see **CLINICAL PHARMACOLOGY**).

Because of reports of adverse eye findings with agents of this class, it is recommended that patients who develop eye complaints during treatment with diflunisal have ophthalmologic studies.

Peripheral edema has been observed in some patients taking diflunisal. Therefore, as with other drugs in this class, diflunisal should be used with caution in patients with compromised cardiac function, hypertension, or other conditions predisposing to fluid retention.

Acetylsalicylic acid has been associated with Reye syndrome. Because diflunisal is a derivative of salicylic acid, the possibility of its association with Reye syndrome cannot be excluded.

Hypersensitivity Syndrome

A potentially life-threatening, apparent hypersensitivity syndrome has been reported. This multisystem syndrome includes constitutional symptoms (fever, chills), and cutaneous findings (see **ADVERSE REACTIONS, Dermatologic**). It may also include involvement of major organs (changes in liver function, jaundice, leukopenia, thrombocytopenia, eosinophilia, disseminated intravascular coagulation, renal impairment including renal failure), and less specific findings (adenitis, arthralgia, myalgia, arthritis, malaise, anorexia, disorientation). If evidence of hypersensitivity occurs, therapy with diflunisal should be discontinued.

Renal Effects

As with other non-steroidal anti-inflammatory drugs, long term administration of diflunisal to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria and proteinuria and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal and renal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with conditions such as renal or hepatic dysfunction, diabetes mellitus, advanced age, extracellular volume depletion from any cause, congestive heart failure, septicemia, pyelonephritis, or concomitant use of any nephrotoxic drug. Diflunisal or other NSAIDs should be given with caution and renal function should be monitored in any patient who may have reduced renal reserve. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

Since diflunisal is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored; a lower daily dosage should be anticipated to avoid excessive drug accumulation.

Information for Patients

Diflunisal, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

NSAIDs (Non-steroidal Anti-inflammatory Drugs) are often essential agents in the management of arthritis and have a major role in the treatment of pain, but they also may be commonly employed for conditions which are less serious.

5

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Diflunisal, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

NSAIDs (Non-steroidal Anti-inflammatory Drugs) are often essential agents in the management of arthritis and have a major role in the treatment of pain, but they also may be commonly employed for conditions which are less serious.

Physicians may wish to discuss with their patients the potential risks (see **WARNINGS, PRECAUTIONS and ADVERSE REACTIONS**) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

Laboratory Tests

Liver Function Tests

As with other non-steroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with diflunisal. Severe hepatic reactions, including jaundice, have been reported with diflunisal as well as with other non-steroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical

6

signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), diflunisal should be discontinued, since liver reactions can be fatal.

Gastrointestinal

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see **WARNINGS, Risk of GI Ulcerations, Bleeding and Perforation with NSAID Therapy**).

Drug Interactions

Oral Anticoagulants

In some normal volunteers, the concomitant administration of diflunisal and warfarin, acenocoumarol, or phenprocoumon resulted in prolongation of prothrombin time. This may occur because diflunisal competitively displaces coumarins from protein binding sites. Accordingly, when diflunisal is administered with oral anticoagulants, the prothrombin time should be closely monitored during and for several days after concomitant drug administration. Adjustment of dosage of oral anticoagulants may be required.

Tolbutamide

In diabetic patients receiving diflunisal and tolbutamide, no significant effects were seen on tolbutamide plasma levels or fasting blood glucose.

Hydrochlorothiazide

In normal volunteers, concomitant administration of diflunisal and hydrochlorothiazide resulted in significantly increased plasma levels of hydrochlorothiazide. Diflunisal decreased the hyperuricemic effect of hydrochlorothiazide.

Furosemide

In normal volunteers, the concomitant administration of diflunisal and furosemide had no effect on the diuretic activity of furosemide. Diflunisal decreased the hyperuricemic effect of furosemide.

Antacids

Concomitant administration of antacids may reduce plasma levels of diflunisal. This effect is small with occasional doses of antacids, but may be clinically significant when antacids are used on a continuous schedule.

Acetaminophen

In normal volunteers, concomitant administration of diflunisal and acetaminophen resulted in an approximate 50% increase in plasma levels of acetaminophen. Acetaminophen had no effect on plasma levels of diflunisal. Since acetaminophen in high doses has been associated with hepatotoxicity, concomitant administration of diflunisal and acetaminophen should be used cautiously, with careful monitoring of patients.

Concomitant administration of diflunisal and acetaminophen in dogs, but not in rats, at approximately 2 times the recommended maximum human therapeutic dose of each (40-52 mg/kg/day of diflunisal/acetaminophen), resulted in greater gastrointestinal toxicity than when either drug was administered alone. The clinical significance of these findings has not been established.

Methotrexate

Caution should be used if diflunisal is administered concomitantly with methotrexate. Non-steroidal anti-inflammatory drugs have been reported to decrease the tubular secretion of methotrexate and to potentiate its toxicity.

Cyclosporine

Administration of non-steroidal anti-inflammatory drugs concomitantly with cyclosporine has been associated with an increase in cyclosporine-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. NSAIDs should be used with caution in patients taking cyclosporine, and renal function should be carefully monitored.

Drug Interactions

Non-steroidal Anti-inflammatory Drugs

The administration of diflunisal to normal volunteers receiving indomethacin decreased the renal clearance and significantly increased the plasma levels of indomethacin. In some patients the combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal hemorrhage. Therefore, indomethacin and diflunisal should not be used concomitantly.

Since no further clinical data are available about the safety and effectiveness of diflunisal when used in combination with other non-steroidal anti-inflammatory drugs, no recommendation for their concomitant use can be made. The following information was obtained from studies in normal volunteers.

Aspirin

In normal volunteers, a small decrease in diflunisal levels was observed when multiple doses of diflunisal and aspirin were administered concomitantly.

Sulindac

The concomitant administration of diflunisal and sulindac in normal volunteers resulted in lowering of the plasma levels of the active sulindac sulfide metabolite by approximately one-third.

Naproxen

The concomitant administration of diflunisal and naproxen in normal volunteers had no effect on the plasma levels of naproxen, but significantly decreased the urinary excretion of naproxen and its glucuronide metabolite. Naproxen had no effect on plasma levels of diflunisal.

Drug/Laboratory Test Interactions

Serum Salicylate Assays

Caution should be used in interpreting the results of serum salicylate assays when diflunisal is present. Salicylate levels have been found to be falsely elevated with some assay methods.

Carcinogenicity: Mutagenicity: ...

7

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Drug/Laboratory Test Interactions

Serum Salicylate Assays

Caution should be used in interpreting the results of serum salicylate assays when diflunisal is present. Salicylate levels have been found to be falsely elevated with some assay methods.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Diflunisal did not affect the type or incidence of neoplasia in a 105-week study in the rat given doses up to 40 mg/kg/day (equivalent to approximately 1.3 times the maximum recommended human dose), or in long-term carcinogenic studies in mice given diflunisal at doses up to 80 mg/kg/day (equivalent to approximately 2.7 times the maximum recommended human dose). It was concluded that there was no carcinogenic potential for diflunisal.

Diflunisal passes the placental barrier to a minor degree in the rat. Diflunisal had no mutagenic activity after oral administration in the dominant lethal assay, in the Ames microbial mutagen test or in the V-79 Chinese hamster lung cell assay.

No evidence of impaired fertility was found in reproduction studies in rats at doses up to 50 mg/kg/day.

Pregnancy

Pregnancy Category C. A dose of 60 mg/kg/day of diflunisal (equivalent to two times the maximum human dose) was maternotoxic, embryotoxic, and teratogenic in rabbits. In three of six studies in rabbits, evidence of teratogenicity was observed at doses ranging from 40 to 50 mg/kg/day. Teratology studies in mice, at doses up to 45 mg/kg/day, and in rats at doses up to 100 mg/kg/day, revealed no harm to the fetus due to diflunisal. Aspirin and other salicylates have been shown to be teratogenic in a wide variety of species, including the rat and rabbit, at doses ranging from 50 to 400 mg/kg/day (approximately one to eight times the human dose). There are no adequate and well-controlled studies with diflunisal in pregnant women. Diflunisal should be used during the first two trimesters of pregnancy only if the potential benefit justifies the potential risk to the fetus. Because of the known effect of drugs of this class on the human fetus (closure of the ductus arteriosus, platelet dysfunction with resultant bleeding, renal dysfunction or failure with oligohydramnios, gastrointestinal bleeding or perforation, and myocardial degenerative changes), use during the third trimester of pregnancy is not recommended.

In rats at a dose of one and one-half times the maximum human dose, there was an increase in the average length of gestation. Similar increases in the length of gestation have been observed with aspirin, indomethacin, and phenylbutazone, and may be related to inhibition of prostaglandin synthetase. Drugs of this class may cause dystocia and delayed parturition in pregnant animals.

Nursing Mothers

Diflunisal is excreted in human milk in concentrations of 2-7% of those in plasma. Because of the potential for serious adverse reactions in nursing infants from diflunisal, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The adverse effects observed following diflunisal administration to neonatal animals appear to be species, age, and dose-dependent. At dose levels approximately 3 times the usual human therapeutic dose, both aspirin (200 to 400 mg/kg/day) and diflunisal (80 mg/kg/day) resulted in death, leukocytosis, weight loss, and bilateral cataracts in neonatal (4 to 5-day old) beagle puppies after 2 to 10 doses. Administration of an 80 mg/kg/day dose of diflunisal to 25-day-old puppies resulted in lower mortality, and did not produce cataracts. In newborn rats, a 400 mg/kg/day dose of aspirin resulted in increased mortality and some cataracts, whereas the effects of diflunisal administration at doses up to 140 mg/kg/day were limited to a decrease in average body weight gain.

Safety and effectiveness in infants and children have not been established, and use of the drug in children below the age of 12 years is not recommended.

ADVERSE REACTIONS

The adverse reactions observed in controlled clinical trials encompass observations in 2,427 patients.

Listed below are the adverse reactions reported in the 1,314 of these patients who received treatment in studies of two weeks or longer. Five hundred thirteen patients were treated for at least 24 weeks, 255 patients were treated for at least 48 weeks, and 46 patients were treated for 96 weeks. In general, the adverse reactions listed below were 2 to 14 times less frequent in the 1,113 patients who received short-term treatment for mild to moderate pain.

Incidence Greater Than 1%

Gastrointestinal

The most frequent types of adverse reactions occurring with diflunisal are gastrointestinal: these include nausea, vomiting, dyspepsia, gastrointestinal pain, diarrhea, constipation, and flatulence.

Psychiatric

Somnolence, insomnia.

Central Nervous System

Dizziness.

Special Senses

Tinnitus

8

tinnitus.

Dermatologic

Rash*.

Miscellaneous

Headache*, fatigue/tiredness.

*Incidence between 3% and 9%. Those reactions occurring in 1% to 3% are not marked with an asterisk.

Incidence Less Than 1 in 100

The following adverse reactions, occurring less frequently than 1 in 100, were reported in clinical trials or since the drug was marketed. The probability exists of a causal relationship between diflunisal and these adverse reactions.

Dermatologic

Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, pruritus, sweating, dry mucous membranes, stomatitis, photosensitivity.

Gastrointestinal

Peptic ulcer, gastrointestinal bleeding, anorexia, eructation, gastrointestinal perforation, gastritis.

Liver function abnormalities; jaundice, sometimes with fever; cholestasis; hepatitis.

Hematologic

Thrombocytopenia; agranulocytosis, hemolytic anemia.

Genitourinary

Dysuria; renal impairment, including renal failure; interstitial nephritis; hematuria; proteinuria.

Psychiatric

Nervousness, depression, hallucinations, confusion, disorientation.

Central Nervous System

Vertigo, light-headedness; paresthesias.

Special Senses

Transient visual disturbances including blurred vision.

Hypersensitivity Reactions

Acute anaphylactic reaction with bronchospasm; angioedema; flushing.

Hypersensitivity vasculitis.

Hypersensitivity syndrome (see **PRECAUTIONS**).

Miscellaneous

Asthenia, edema.

Causal Relationship Unknown

Other reactions have been reported in clinical trials or since the drug was marketed, but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, that possibility cannot be excluded. Therefore, these observations are listed to serve as alerting information to physicians.

Respiratory

Dyspnea.

Cardiovascular

Palpitation, syncope.

Musculoskeletal

Muscle cramps.

Genitourinary

Nephrotic syndrome.

Miscellaneous

Chest pain.

A rare occurrence of fulminant necrotizing fasciitis, particularly in association with Group A β -hemolytic streptococcus, has been described in persons treated with non-steroidal anti-inflammatory agents, including diflunisal, sometimes with fatal outcome (see also **PRECAUTIONS, General**).

Potential Adverse Effects

In addition, a variety of adverse effects not observed with diflunisal in clinical trials or in marketing experience, but reported with other non-steroidal analgesic/anti-inflammatory agents, should be considered potential adverse effects of diflunisal.

OVERDOSAGE

Cases of overdosage have occurred and deaths have been reported. Most patients recovered without evidence of permanent sequelae. The most common signs and symptoms observed with overdosage were drowsiness, vomiting, nausea, diarrhea, hyperventilation, tachycardia, sweating, tinnitus, disorientation, stupor and coma. Diminished urine output and cardiorespiratory arrest have also been reported. The lowest dosage of diflunisal at which a death has been reported was 15 grams without the presence of other drugs. In a mixed drug overdose, ingestion of 7.5 grams of diflunisal resulted in death.

In the event of overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage, and the patient carefully observed and given symptomatic and supportive treatment. Because of the high degree of protein binding, hemodialysis may not be effective.

The oral LD₅₀ of the drug is 500 mg/kg and 826 mg/kg in female mice and female rats respectively.

DOSEAGE AND ADMINISTRATION

Concentration-dependent pharmacokinetics prevail when diflunisal is administered; a doubling of dosage produces a greater than doubling of drug accumulation. The effect becomes more apparent with repetitive doses.

For mild to moderate pain, an initial dose of 1000 mg followed by 500 mg every 12 hours is recommended for most patients. Following the initial dose, some patients may require 500 mg every 8 hours.

A lower dosage may be appropriate depending on such factors as pain severity, patient response, weight, or advanced age; for example, 500 mg initially, followed by 250 mg every 8-12 hours.

For osteoarthritis and rheumatoid arthritis, the suggested dosage range is 500 mg to 1000 mg daily in two divided doses. The dosage of diflunisal may be increased or decreased according to patient response.

Causal Relationship Unknown

Other reactions have been reported in clinical trials or since the drug was marketed, but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, that possibility cannot be excluded. Therefore, these observations are listed to serve as alerting information to physicians.

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A lower dosage may be appropriate depending on such factors as pain severity, patient response, weight, or advanced age; for example, 500 mg initially, followed by 250 mg every 8-12 hours.

For osteoarthritis and rheumatoid arthritis, the suggested dosage range is 500 mg to 1000 mg daily in two divided doses. The dosage of diflunisal may be increased or decreased according to patient response.

Maintenance doses higher than 1500 mg a day are not recommended.

Diflunisal may be administered with water, milk or meals. Tablets should be swallowed whole, not crushed or chewed.

HOW SUPPLIED

Diflunisal Tablets, USP 250 mg are unscored, capsule shaped, white, film-coated tablets imprinted "DAN 5835" supplied in bottles of 30, 60, 100, 500 and 1000.

Diflunisal Tablets, USP 500 mg are unscored, capsule shaped, white, film-coated tablets imprinted "DAN 5836" supplied in bottles of 30, 60, 100, 500 and 1000.

Dispense in a well-closed container with a child-resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription.

Manufactured by:
DANBURY PHARMACAL, INC.
Danbury, CT 06810

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074400

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO 13
2. ANDA 74-400
3. NAME AND ADDRESS OF APPLICANT
Schein Pharmaceutical
Attention: William R. McIntyre
131 West Street
Danbury, CT 06810
4. LEGAL BASIS FOR SUBMISSION Dolobid® (Merck)
5. SUPPLEMENT(s) N/A
6. PROPRIETARY NAME N/A
7. NONPROPRIETARY NAME Diflunisal Tablets, USP
8. SUPPLEMENT(s) PROVIDE(s) FOR N/A
9. AMENDMENTS AND OTHER DATES
08/05/93 Original submission
04/04/94 NA Letter (chemistry & labeling)
08/24/95 Correspondence
04/04/96 Correspondence
04/30/96 Amendment *** THIS REVIEW ***
11/20/96 Amendmend (labeled)
06/27-97 Telephone Amendment
10. PHARMACOLOGICAL CATEGORY Analgesic, Anti-inflammatory
11. Rx or OTC
Rx
12. RELATED IND/NDA/DMF(s)
13. DOSAGE FORM
Tablets
14. POTENCY
250 & 500 mg
15. CHEMICAL NAME AND STRUCTURE
2',4'-Difluoro-4-hydroxy-3-biphenylcarboxylic acid
C₁₃H₈F₂O₃ Mol. wt. 250.20 [22494-42-4]
16. RECORDS AND REPORTS N/A
17. COMMENTS Commitments were obtained on the issues raised in the audit, see amendment dated 6-27-97.
18. CONCLUSIONS AND RECOMMENDATIONS
Recommend: APPROVAL.
19. REVIEWER: J. L. Smith DATE COMPLETED: 09/20/96

cc: ANDA
DUP Jacket
Division File

Endorsements:

HFD-623/J.Smith/9-20-96

HFD-623/V.Sayeed, Ph.D./9-26-96

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F/T by: bc/7-1-97

7/2/97

7/2/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074400

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA#: 74-400

SPONSOR: Danbury Pharmacal

DOSAGE FORM: Diflunisal Tablets

STRENGTHS(s): 500 mg.

TYPE OF STUDY: Single dose, Fasting and Non-fasting Studies

STUDY SITE:

STUDY SUMMARY: The results of a fasting bioequivalence study conducted in 24 healthy male volunteers comparing Danbury's diflunisal 500 mg tablet and Merck Sharp and Dohme's Dolobid^R 500 mg tablet indicate that the rate and extent of absorption of the test product were similar to those of the reference product. The 90% confidence intervals for the log-transformed AUC_{0-t} , AUC_{inf} and C_{max} data were within the acceptable range of 80-125%. In addition, the analysis of variance revealed no formulation differences or sequence effects for these three parameters. The result of a non-fasting study comparing the bioavailability of the test and the reference product indicate that following their administration after a standardized breakfast, mean AUC and C_{max} values of the test product were within 20% of those of the reference product. These studies demonstrate that Danbury's diflunisal 500 mg tablet is bioequivalent to the reference product, Dolobid^R 500 mg tablet, manufactured by Merck Sharp and Dohme.

DISSOLUTION: The results of *in vitro* dissolution testing conducted using the USP method indicated that greater than _____ of the labeled amount of diflunisal in the test product was dissolved in 30 minutes. The dissolution testing meets USP/FDA specifications.

PRIMARY REVIEWER: Gur J.P. Singh, Ph.D

BRANCH: II

INITIAL: _____

DATE 5/19/94

BRANCH CHIEF: Rabindra N. Patnaik, Ph.D

BRANCH: II

INITIAL: _____

DATE 5/19/94

ACTING DIRECTOR, DIVISION OF BIOEQUIVALENCE: Ramakant M. Mhatre, Ph.D

INITIAL: _____

DATE 6/26/94

ASSOCIATE DIRECTOR FOR SCIENCE, CDER, FDA: Roger L. Williams, M.D.

INITIAL: _____

DATE 7/22/94

JUN 26 1994

Diflunisal

Tablets, 250 mg and 500 mg

ANDA # 74-400

Reviewer: Gur J.P. Singh

File # 74400SDW.893

Danbury Pharmacal

131 West Street

Danbury, CT 06810

Submission Dates:

August 5, 1993, February 5, 1994
and April 14, 1994.

Review of Two Bioequivalence Studies (Fasting and Non-fasting), Dissolution Data and a waiver request

On August 5, 1993, this firm submitted an application containing data from bioequivalence studies (both fasting and non-fasting) on its diflunisal 500 mg tablets and the reference product, Merck Sharp & Dohme's Dolobid^R 500 mg tablets. The ANDA also contained dissolution data for these products and a request for the waiver of *in vivo* bioequivalence requirements for diflunisal 250 mg tablets. Based on the preliminary review of this application, the firm was advised to submit a diskette containing the pharmacokinetic data and provide information related to the analytical method validation. These items were submitted on February 5 and April 14, 1994, respectively. This review is based on all data submitted, hitherto.

Introduction

Diflunisal, 2',4'-difluoro-4hydroxy-3-biphenylcarboxylic acid, is a nonsteroidal drug with analgesic, antiinflammatory and antipyretic properties. The reference product is marketed as Dolobid^R 250 mg and 500 mg tablets by Merck Sharp & Dohme. It is indicated for treatment of pain, osteoarthritis and rheumatoid arthritis.

Following oral administration, diflunisal is completely absorbed with peak plasma concentration occurring between 2-3 hours. Due to inhibition of plasma clearance by one of its metabolites, acylglucoronide), plasma disposition of this drug is dose dependent; a doubling dose produces greater than doubling of drug accumulation. Such concentration-dependent accumulation is more pronounced following multiple dosing. Thus peak plasma concentrations of $41 \pm 11 \mu\text{g/mL}$, $87 \pm 17 \mu\text{g/mL}$ and $124 \pm 11 \mu\text{g/mL}$ were observed following administration of single doses of 250 mg, 500 mg and 1000 mg respectively. On the other hand, following b.i.d. administration of diflunisal 250 mg and 500 mg, mean peak plasma levels of $56 \pm 14 \mu\text{g/mL}$ and $190 \mu\text{g/mL}$ were observed.

More than 99% of diflunisal in plasma is bound to proteins. This drug is excreted in urine as two soluble glucuronide conjugates accounting for 90% of the administered dose.

A. Fasting Bioequivalence Study

A-1. **OBJECTIVE:** The purpose of this study was to determine the bioequivalence of Danbury Pharmacal's diflunisal 500 mg tablets and Merck Sharp & Dohme's Dolobid^R 500 mg tablets in a single dose, two-treatment, two-period, crossover design with a washout period of seven days between two doings..

A-2. STUDY SITE, INVESTIGATORS AND DATES:

Clinical and Analytical site: The clinical study and sample analyses were conducted at

Medical Director:

Analytical Director:

Study Protocol: Protocol (#1251, pp 422-435, vol 1.2) used for this study was approved by the Institutional Review Board

Dosing Dates: For subject #1-24: Phase I - September 20, 1992, Phase II - September 27, 1992.

For subject #25-27: Phase I - September 27, 1992 , Phase II - October 4, 1992.

Analytical Dates: October 9-19, 1992.

A-3. SUBJECT SELECTION:

Twenty eight (28) healthy male volunteers were enrolled for this study. The average age and weight of these volunteers were 28 years (range = 18-37) and 73 kg (range = 55-87) respectively. All volunteers were within 10% of their ideal body weight. Subjects who entered this study were selected on the basis of their acceptable medical history, physical examination and normal clinical laboratory tests for hematopoietic, hepatic and renal functions.

Subjects were excluded from this study based on the following criteria:

- * Cardiovascular, hepatic, renal, CNS or hematological, gastrointestinal disease or condition (s) that would affect the absorption of drugs.
- * Clinically significant illness during four weeks preceding this study.
- * Alcohol abuse, regular medication or participation in a clinical trial with an investigational drug within 30 days preceding the study.
- * Use of systemic medication including over-the-counter preparations within 14 days preceding the study.
- * Use of drugs similar to diflunisal within 30 days before the study start.

- * History or presence of asthma or allergic rhinitis known to be exacerbated by nonsteroidal antiinflammatory agents.
- * Hypersensitivity to diflunisal, ASA or related products.

A-4. STUDY DESIGN: The clinical study was conducted as a single dose randomized, two treatment, two-period crossover evaluation with the following subject randomization:

<u>TREATMENT-SEQUENCE</u>		<u>SUBJECT NUMBER</u>
<i>Phase I</i>	<i>Phase II</i>	
A	B	1,3,5,7,10,12,13,16,18,19, 20,23,,26,27.
B	A	2,4,6,8,9,11,14,15,21,22,24,25.

(Subject #17 was dropped because of fainting prior to dosing, and subject #28 did not show up for the study).

Where:

- A: Diflunisal tablets 1x500 mg, Danbury Pharmacal, Inc. (lot # 08510C, Lot Size -
- B: Dolobid^R tablets 1x500 mg, Merck Sharp & Dohme (Lot #T0894, Lot Size - Commercial lot, Expiry Date - June, 1996).

A-5. DOSING AND MEALS:

After an overnight (9 hours) fast, each drug was given orally with 240 mL of water. Water was provided *ad libitum* 1.0 hour predose and 2.0 hour post dose. Standard meals were served at 4.5, 9.5 and 15.0 hours after dosing.

A-6. SAMPLE COLLECTION AND STORAGE:

Serial blood samples (7 mL) were collected using EDTA-containing vacutainers at predose (0-hr) and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours after dosing (1x7 mL). Thus a total of 126 mL blood was drawn from each subject during a particular phase of the study. Blood samples were centrifuged within 15 minutes of venipuncture, and plasma separated and stored at $-25 \pm 5^{\circ}\text{C}$ until assayed.

A-7. ANALYTICAL PROCEDURE (Not to be released under FOI):

A-8. PHARMACOKINETIC DATA ANALYSIS: Area under the plasma concentration curve from zero to the last measurable concentration (AUC_{0-t}) was calculated using the trapezoidal integration. Extrapolation of the AUC_{0-t} from last measured concentration to infinity to yield AUC_{inf} was accomplished by addition of the value obtained by dividing this concentration with the elimination rate constant as calculated for each curve. Other pharmacokinetic parameters determined include C_{max} , T_{max} , elimination $t_{1/2}$ and K_{el} . Statistical analyses of pharmacokinetic data were performed using SAS version 6.06 (SAS Institute Inc, Cary, NC). The analysis of variance with subjects, periods and drugs as factors and sequence as between subject factor was applied to diflunisal bioavailability parameters and its plasma concentrations at each sampling

time point. Statistical analyses of pharmacokinetic data were conducted using the t-test method to determine, at $\alpha = 0.05$ and $\beta = 0.20$, differences between diflunisal formulations in AUC_{0-t} , AUC_{inf} and C_{max} .

A-9. MISCELLANEOUS:

INSTITUTIONAL REVIEW BOARD: The protocol and bioequivalence study were approved by the Institutional Review Board

CONSENT FORM: A copy of the volunteer informed consent form used in this study is given on pages 445-448 (vol 1.2).

A-10. RESULTS AND DISCUSSION:

CLINICAL STUDY CONDUCT: Of the twenty eight (28) volunteers enrolled for this study, twenty six (26) subjects were dosed because volunteer #17 fainted before dosing and subject #28 did not show up for the study. All 26 subjects completed the study. Based on the protocol, the firm has analyzed samples from 24 subjects which includes subject #25 who was taken in place of subject #17. Dosing dates for subject #25 were different from rest of the subjects. The reviewer has examined the effect on the outcome of this study of inclusion/exclusion of this volunteer's data. During the conduct of this study, few protocol deviations occurred including a one-minute delay in blood sampling of subject #11 (5-hr sample) and #19 (3-hr sample), and failures of subject #13 and #15 to return for post study clinical laboratory testing. No adverse reactions/events were reported in this study.

PHARMACOKINETIC PROFILE: Diflunisal plasma concentration profiles of various subjects are given on pages 303-306 (vol 1.2). These are complete data sets, there are no missing values. Figures showing individual subject diflunisal plasma profiles are given on pages 338-361 (vol 1.2). These figure indicate that the plasma disposition of diflunisal following the administration of the test and reference products was similar except in subject #1 and #19.

The reviewer has performed spot-check calculations to determine the accuracy of the AUC_{0-t} and AUC_{inf} values given in this application. The results of these calculations, given below, employing the test product data indicate good agreement between reviewer's calculations and the data reported by the firm.

Subject #	Reviewer(A)		Sponsor (B)		A/B	
	AUC_{0-t}	AUC_{inf}	AUC_{0-t}	AUC_{inf}	AUC_{0-t}	AUC_{inf}
3	893.36	950.41	893.36	952.05	1.00	0.99
8	775.52	786.89	775.52	786.82	1.00	1.00
14	635.56	641.64	635.56	641.61	1.00	1.00
22	489.41	497.98	489.41	498.07	1.00	0.99

The foregoing calculations demonstrated an acceptable accuracy of AUC_{0-t} and AUC_{inf} values given in this application. Furthermore, the AUC_{0-t}/AUC_{inf} ratios indicate that the AUC_{0-t} will cover most of the areas; mean AUC_{0-t}/AUC_{inf} ratios for the test product and the reference products was 0.95 and 0.95 respectively (pp 307-308, vol 1.2).

Results of diflunisal fasting bioequivalence study are summarized in Table 2 (attachment). Diflunisal mean plasma concentrations are given in table 2 and Figure 1. These data indicate that with the exception of 0.5 and 1 hour samples, diflunisal plasma concentrations following administration of the test product was within 20% of that of the reference product.

Both the test and reference drug products were readily absorbed with a T_{max} values of 2.58 and 2.65 hours, respectively. The test product had an AUC_{0-t} of 751.81 $\mu\text{g/mL}\cdot\text{hr}$ and an AUC_{inf} of 786.56 $\mu\text{g/mL}\cdot\text{hr}$ which were 4% and 5% lower than the reference product's respective values. Based on reviewer's calculations using the log transformed data, the 90% confidence intervals for these two parameters are in the range of 89.34 - 103.66%

The C_{max} mean value for the test product was 2% lower than that of the reference product. The C_{max} 90% confidence intervals are in the range of 91.16 - 105.63% (Table 2). The average $t_{1/2}$ of the test product was 2% lower and its K_{el} was 1% higher than that of the reference product. The individual subject values of all these parameters are given on pages 307-308 (vol 1.2), and with the exception of AUC data for subject #1 (Reference), significant deviations from mean values were not observed.

Statistical analysis of data did not show significant sequence and/or period effects for AUC_{0-t} , AUC_{inf} and C_{max} data. The 90% confidence intervals for these parameters were within the acceptable range of 80-125%. Therefore, the results of this study indicate that under fasting conditions, Danbury's diflunisal 500 mg tablet is bioequivalent to the reference product, Dolobid^R 500 mg tablet.

As mentioned above, subject # 25 was dosed on days different from the remaining 23 volunteers. Therefore, the reviewer has examined the effect of exclusion of this subject's data on the outcome of this study. Data given in table 2 show that the 90% confidence intervals for AUC_{0-t} , AUC_{inf} and C_{max} log transformed data remain within the acceptable range of 80-125% with or without data for subject #25.

The individual subject ratios for AUC_{0-t} , AUC_{inf} , and C_{max} are given on pages 309, 315 and 321 (vol 1.2), respectively. These data indicate the based on mean of individual ratios, test product's AUC_{0-t} and AUC_{inf} were 3% lower than that of the reference product whereas there was no difference in the C_{max} values of these products.

B. Non-fasting Bioavailability Study

B-1. OBJECTIVE: The purpose of this study was to compare the bioavailability of Danbury Pharmacal's diflunisal 500 mg tablets and Merck Sharp & Dohme's Dolobid^R 500 mg tablets in fed volunteers.

B-2. STUDY SITE, PERSONNEL: Same as that mentioned above for the fasting study.

Dosing Dates: Phase I - January 23, 1993, Phase II - January 30, 1993, phase III - February 6, 1993.

Sample Analysis Dates: February 22 - March 12, 1993

Study protocol: The protocol (#1280, pp 1250-1262, vol 1.4) for this study was approved by the Institutional Review Board.

B-3. SUBJECT SELECTION: Twenty one (21) healthy male volunteers were enrolled for this study. The mean age and weights of these subjects were 30 years (range = 18-43) and 77 kg (range = 68-92). The subject selection criteria for this study (pp 1256-57, vol 1.4)) were the same as those mentioned above for the fasting study.

B-4. STUDY DESIGN: This study was conducted as a single dose, randomized, three-treatment, three-period, six-sequence crossover evaluation. A one-week washout period separated the dosing days. Volunteers were dosed based on the following randomization:

<u>TREATMENT-SEQUENCE</u>			<u>SUBJECTS NUMBER</u>
<i>Phase I</i>	<i>Phase II</i>	<i>Phase III</i>	
A	B	C	4, 6, 12
A	C	B	3, 14, 17, 21
B	A	C	15, 16, 18
B	C	A	5, 11, 7
C	A	B	2, 9, 10, 20
C	B	A	1, 8, 13, 19

A = Diflunisal tablets, 1x500, Lot #08510C, Danbury Pharmacal Inc. administered after overnight fast.

B = Diflunisal tablets, 1x500, Lot #08510C, Danbury Pharmacal Inc. administered within five minutes of ingesting a standardized breakfast.

C = Dolobid^R tablets, 1x500 mg, Lot #T0894, Merck Sharp & Dohme, administered within five minutes of ingesting a standardized breakfast.

(Lot numbers for drug products administered in this study were the same as those used for the fasting study).

B-5. DOSING AND MEALS: After an overnight fast (Regimen A) and within five minutes of ingesting a standardized breakfast (Regimen B and C), subjects were given a single oral dose (1x500 mg) of the assigned formulation, with 240 mL of water, according to the randomization scheme outlined above. The composition of the breakfast given before dosing regimens B and C was as follows: *180 mL orange juice, 240 mL whole milk, 1 fried egg, 3 strips of bacon, one buttered english muffin, 1 slice of American cheese, and a 4-ounce serving of hash brown potatoes.* Standard meals were provided at 4.5 and 10 hr after dosing and at appropriate times thereafter, meal plans were identical for all three phases of this study.

B-6. SAMPLE COLLECTION AND STORAGE: Same as mentioned for the fasting study.

B-7. ANALYTICAL PROCEDURE: The method employed for sample extraction and analysis was the same as that mentioned above (fasting study).

B-8. PHARMACOKINETIC DATA ANALYSIS: Pharmacokinetic parameters determined and the methods used for their calculation and statistical analysis were the same as those employed for the fasting study.

B-9. RESULTS AND DISCUSSION:

CLINICAL STUDY CONDUCT: A total of twenty one (21) subjects were dosed in phase I of this study, and twenty subjects completed the crossover study. Subject # 9 did not complete all phases of the study. The firm has reported pharmacokinetic data for 18 subjects, as specified in the protocol. In this investigation, protocol deviations related to 1-2 minutes delay in taking two blood samples were reported. No adverse events were reported in this study..

ACCEPTABILITY OF THE ANALYTICAL METHOD: The standard curve, controls and

PHARMACOKINETIC PROFILE: Diflunisal plasma concentration profiles of various subjects are given on pages 1106-1111 (vol 1.4). These are complete data sets, there are no missing values. Figures showing individual subject diflunisal plasma profiles are given on pages 1174-1191 (vol 1.4). These graphs indicate that under fed conditions, the plasma disposition of diflunisal following the administration of the test and reference products was similar except in subject #5 and 14.

Like the fasting study, the mean AUC_{0-t}/AUC_{inf} ratios for the test product and the reference products were 0.95 and 0.95. These AUC_{0-t}/AUC_{inf} ratios indicate that AUC was within 89-95% of AUC_{inf} for all determinations.

Results of the non-fasting diflunisal bioavailability study are summarized in Table 4. (attachment). Diflunisal mean plasma concentrations are given in this table and Figure 2. These data indicate that, under non-fasting conditions, with exception of 0.5-2.0 hours, diflunisal plasma concentrations following administration of the test product were within 20% of that of the reference product.

Under nonfasting conditions, the test and reference drug products exhibited identical mean T_{max} values of 3.83 hours. The test product had an AUC_{0-t} of 774.27 $\mu\text{g/mL}\cdot\text{hr}$ and an AUC_{inf} of 819.04 $\mu\text{g/mL}\cdot\text{hr}$ which were 0.05% and 1% higher than the respective reference product's values. C_{max} mean value for the test product was 2% lower than that of the reference product. These data indicate that under non-fasting conditions the bioavailability of the test product was within $\pm 20\%$ of that of the reference product.

The individual subject ratios for AUC_{0-t} , AUC_{inf} and C_{max} under nonfasting conditions are given on pages 1115, 1128 and 1141 (vol 1.4), respectively. These data indicate the based on mean of individual ratios, test products AUC_{0-t} and AUC_{inf} were 0.7% and 1.5% higher than that of the reference product. Based on these ratios, test product's C_{max} was 1.2% lower than that of the reference product.

C. *In Vitro* Dissolution Testing

The firm has submitted dissolution data for its drug products, diflunisal 250 mg and 500 mg tablets and corresponding strengths of the reference product, Dolobid^R (pp 259-268, vol 1.2). The details of dissolution testing are given in the accompanying dissolution data sheet (Table 5). The results of *in vitro* dissolution testing indicate that greater than of diflunisal was dissolved from the test product within 45 minutes. The dissolution profiles of the test and the reference products were similar. Drug products' lots used for *in vitro* dissolution testing were identical to those used for *in vivo* bioequivalence studies.

D. Waiver Request

The firm has submitted a request for waiver of *in vivo* bioequivalence requirements for its diflunisal 250 mg tablets. It has met requirements of *in vivo* bioequivalence and *in vitro* dissolution testing on its diflunisal 500 mg tablets. It has also demonstrated that the composition of its diflunisal 250 mg tablets is proportional to that of its 500 mg diflunisal tablets (Table 6), which underwent bioequivalence testing. The dissolution profiles of diflunisal 250 mg tablets is similar to that of Dolobid^R 250 mg tablets. Therefore, the waiver of *in vivo* bioequivalence requirements for the diflunisal 250 mg tablets may be granted.

E. Comments

This firm has conducted a fasting and a non-fasting bioequivalence study of its diflunisal 500 mg tablet and the reference drug product, Dolobid^R 500 mg tablet. The reviewer's comments on this application are as follows:

A. FASTING STUDY

- A-1. Of the twenty eight (28) volunteers enrolled for this study, twenty six (26) subjects were dosed because volunteer #17 fainted before dosing, and subject #28 did not show up for the study. All 26 subjects completed the study, and during the conduct of this study no adverse reactions/events were reported.
- A-2. In this study, diflunisal AUC_{0-t} and AUC_{inf} were 4 % and 5 % lower than the respective values for the reference product, Dolobid^R. Test product's C_{max} was 2 lower than that of the reference product. Based on reviewer's calculations, the 90 % confidence intervals for the log transformed data of these parameters were within the acceptable range 80-125 %. There were no statistically significant treatment, period or sequence effects for AUC_{0-t} and AUC_{inf} and C_{max} .
- A-3. Based on the protocol outline, bioavailability comparisons were made using the 24 subject's data. These subjects also included volunteer #25 whose dosing dates were different from other subjects. Therefore, ANOVA was also performed on the log transformed parametric data with or without such data for this subject. The results of this data analysis indicated that the test product remains bioequivalent to the reference product with or without inclusion of subject #25 data because, in either case, the confidence intervals for the AUC and C_{max} data remain within the acceptable limit of 80-125 %.
- A-4. The results of this study demonstrate that under non-fasting conditions, Danbury's diflunisal 500 mg tablet is bioequivalent to the reference product, Dolobid^R 500 mg tablet.

B. NON-FASTING STUDY

- B-1. A total of twenty one (21) subjects were dosed in phase I of this study, and twenty subjects completed the crossover study. Subject # 9 dropped out during phase II. The firms has reported pharmacokinetic data on 18 subjects, as specified in the protocol. No adverse events were reported in this study.
- B-2. In this study, the test product's mean AUC_{0-t} and AUC_{inf} values were 0.05 and 1 % higher than those the reference product. The C_{max} value of the test product was 2 %

lower than that of the reference product. The test/reference ratios for mean AUC_{0-t} , AUC_{inf} and C_{max} are within the acceptable range (*i. e.* the differences between two products are within $\pm 20\%$).

- B-3. Under non-fasting conditions, diflunisal T_{max} for the test and reference products were identical (3.83 hours). A comparison of the fasting and nonfasting condition data of the test product indicate that under fed conditions, the rate of diflunisal absorption may be slower (as indicated by a 19% drop in the C_{max} value and T_{max} prolongation by 1.72 hours). The effect of food on the extent of absorption (AUC_{0-t} and AUC_{inf}) was less pronounced.

C. DISSOLUTION TESTING AND WAIVER REQUEST

- C-1. By conducting *in vitro* dissolution studies of its diflunisal 250 and 500 mg tablets, in accordance with USP specifications, the firm has demonstrated that greater than 80% of the drug is dissolved in 30 minutes. The lots of test and reference products employed in the *in vitro* dissolution testing were identical to those used for the *in vivo* bioequivalence studies. The *in vitro* dissolution data for the test product are acceptable.
- C-2. The firm has met requirements of *in vivo* bioequivalence and *in vitro* dissolution testing on its diflunisal 500 mg tablets. It has also demonstrated that the composition of its diflunisal 250 mg tablets is proportional to that of its 500 mg diflunisal tablets, which underwent bioequivalence testing. The dissolution profiles of diflunisal 250 mg tablets is similar to that of Dolobid^R 250 mg tablets. Therefore, the request for the waiver of *in vivo* bioequivalence requirements for diflunisal 250 mg tablets may be granted.

F. Recommendations

1. The *in-vivo* bioequivalence study conducted under fasting condition by Danbury Pharmacal on its diflunisal 500 mg tablet, lot #08510C, comparing it to the reference product Dolobid^R 500 mg tablet, lot #T0894, manufactured by Merck Sharp & Dohme Laboratories, has been found to be acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Danbury Pharmacal's diflunisal 500 mg tablets are bioequivalent to Dolobid^R 500 mg tablets, manufactured by Merck Sharp & Dohme laboratories.
2. The *in-vivo* bioavailability study conducted under non-fasting conditions, by Danbury Pharmacal on its diflunisal 500 mg tablets, lot # 08510C, comparing it to the reference product Dolobid^R 500 mg tablets, lot # T0894, manufactured by Merck Sharp & Dohme Laboratories, has been found to be acceptable to the Division of Bioequivalence. The study demonstrates that under the non-fasting conditions, the bioavailability of Danbury Pharmacal's diflunisal 500 mg tablets is similar to that of the reference product, Dolobid^R 500 mg tablets manufactured by Merck Sharp & Dohme laboratories.
3. The *in vitro* dissolution testing conducted by Danbury Pharmacal Ltd on its diflunisal 250 and 500 mg tablets, lot #08645C and #08510C, is acceptable. The firm has conducted an acceptable single dose *in vivo* bioequivalence study under fasting condition and an acceptable *in vivo* bioavailability study under non-fasting conditions comparing 500 mg tablet of the test product with the 500 mg tablet of the reference product, Dolobid^R, manufactured by Merck Sharp and Dohme Laboratories. The formulation for diflunisal 250 mg is proportionally similar to the 500 mg tablet of the test product which underwent bioequivalence testing. The waiver of *in vivo* bioequivalence study requirements for 250 mg tablets of the test product is granted. The 250 mg tablet of the test product is therefore deemed bioequivalent to the 250 mg tablet of the reference product, Dolobid^R, manufactured by Merck Sharp and Dohme.
4. The dissolution testing should be incorporated into firm's manufacturing and stability programs. The dissolution should be conducted in 900 mL of 0.1 M Tris buffer, pH 7.2, using apparatus II (paddles) at 50 rpm. The dissolution testing should meet the following specifications.

Not less than of the labeled amount of diflunisal is dissolved from the dosage form in 30 minutes.

5. From the bioequivalence point of view, the firm has met the requirements for *in vivo* bioequivalence and *in vitro* dissolution testing.

The firm should be informed of the above recommendations.

Gur J.P. Singh, Ph.D
Review Branch II
Division of Bioequivalence.

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CONCUR.

DATE: 6/26/94

Ramakant M. Mhatre, Ph.D.
Director
Division of Bioequivalence.

GJPSINGH/ 5/17/94/74400SDW.893

cc: ANDA # 74400 (original, duplicate), HFD-630 (OGD)HFC-130 (Jallen), HFD-600 (Hare),
HFD-344 (CVishwanathan), HFD-655 (Patnaik, Singh), Drug file, Division file.

TABLE 1

Reproducibility of the analytical technique employed for determination of diflunisal plasma concentrations in the fasting study (ANDA #74400).

NOMINAL CONC. (μ G/mL)	N	ASSAYED CONC. (μ g/mL)	ACCURACY (% OF NOMINAL)	PRECISION (% CV)
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A. INTERDAY REPRODUCIBILITY

Quality Control Samples

Calibration Standards

TABLE 2

Plasma concentrations and pharmacokinetic parameters of diflunisal in the fasting study (ANDA #74400). Data are given as arithmetic mean and standard deviation.

Time (hr)	TEST		REF		TEST/REF
	Mean	S.D	Mean	S.D.	
0	0.00	0.00	0.00	0.00	-
0.5	14.37	11.53	6.73	8.09	2.14
1	33.87	25.08	26.50	19.68	1.28
1.5	49.53	24.10	43.19	22.70	1.15
2	56.46	22.90	55.56	20.96	1.02
2.5	57.44	20.13	59.67	19.96	0.96
3	55.38	17.49	59.69	16.66	0.93
3.5	51.18	15.58	57.59	12.24	0.89
4	51.97	9.54	56.77	11.75	0.92
5	45.63	7.37	48.26	10.41	0.95
6	39.26	7.67	41.35	9.29	0.95
8	29.53	6.22	31.31	6.84	0.94
10	25.42	4.87	26.77	6.82	0.95
12	22.00	4.43	22.95	5.82	0.96
16	16.55	4.21	17.65	4.77	0.94
24	10.22	3.12	11.28	5.06	0.91
36	4.95	2.21	5.25	2.73	0.94
48	2.07	1.29	2.27	1.60	0.91

Parameter**ALL SUBJECTS****90% Conf. Intl***

AUC _{0-t} ($\mu\text{g/mL}\cdot\text{hr}$)	751.81 \pm 152.44	786.79 \pm 200.43	0.96	89.34 - 103.66
AUC _{inf} ($\mu\text{g/mL}\cdot\text{hr}$)	786.56 \pm 173.75	827.93 \pm 226.25	0.95	89.00 - 103.17
C _{max} ($\mu\text{g/mL}$)	69.48 \pm 12.72	70.70 \pm 13.41	0.98	91.16 - 105.63
T _{max} (hr)	2.58 \pm 1.00	2.65 \pm 0.89	0.97	
t _{1/2}	10.42 \pm 2.10	10.58 \pm 2.32	0.98	
K _{el} (hr ⁻¹)	0.069 \pm 0.013	0.068 \pm 0.013	1.01	

SUBJECT #25 EXCLUDED

AUC _{0-t} ($\mu\text{g/mL}\cdot\text{hr}$)	754.03 \pm 155.44	789.24 \pm 204.26	0.95	89.06 - 104.17
AUC _{inf} ($\mu\text{g/mL}\cdot\text{hr}$)	788.63 \pm 177.35	830.47 \pm 230.98	0.95	88.72 - 103.66
C _{max} ($\mu\text{g/mL}$)	69.58 \pm 12.99	70.75 \pm 13.71	0.99	90.85 - 106.12

* The 90%-CI are based on ANOVA performed by the reviewer using log transformed data.

TABLE 3

Reproducibility of the analytical technique employed for determination of diflunisal plasma concentrations in the non fasting study (ANDA #74400)

NOMINAL CONC. (μ G/mL)	N	ASSAYED CONC. (μ g/mL)	ACCURACY (% OF NOMINAL)	PRECISION (%CV)
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A. INTERDAY REPRODUCIBILITY

Quality Control Samples

Calibration Standards

TABLE 4

Plasma concentrations and pharmacokinetic parameters of diflunisal in the non-fasting study (ANDA #74400). Data are given as arithmetic mean and standard deviation.

Time (hr)	TEST-FAST (A)		TEST-FED (B)		REF-FED (C)		B/A	B/C	A/C
	Mean	S.D.	Mean	S.D.	Mean	S.D.			
0	0.00	0.00	0.00	0.00	0.00	0.00	-	-	-
0.5	22.96	16.95	3.84	7.78	0.55	1.16	0.13	6.98	41.75
1	47.76	21.52	15.88	19.02	6.20	6.00	0.33	2.56	7.70
1.5	62.96	18.30	32.12	21.57	21.10	17.66	0.51	1.52	2.98
2	65.00	15.34	42.05	19.91	33.62	22.21	0.65	1.25	1.93
2.5	64.40	12.92	45.03	15.57	40.10	24.60	0.70	1.12	1.61
3	57.81	10.14	47.44	17.37	46.30	20.46	0.82	1.02	1.25
3.5	55.23	10.04	47.82	14.42	47.85	17.22	0.83	1.00	1.15
4	53.07	9.84	46.08	11.53	49.27	14.07	0.87	0.94	1.08
5	46.66	9.71	51.01	12.01	51.54	11.84	1.09	0.99	0.91
6	39.60	8.59	43.33	8.95	44.67	8.16	1.09	0.97	0.89
8	32.59	6.43	33.38	6.45	34.14	6.11	1.02	0.98	0.95
10	27.35	5.60	28.60	4.91	28.72	4.57	1.05	1.00	0.95
12	24.23	4.94	24.46	4.11	24.86	4.43	1.01	0.98	0.97
16	18.78	3.93	19.98	3.94	19.54	3.66	1.06	1.02	0.96
24	11.27	2.86	11.25	1.27	11.47	2.99	0.99	0.98	0.98
36	5.61	1.95	5.59	1.81	5.91	1.92	0.99	0.95	0.95
48	2.46	1.14	2.64	1.27	2.43	1.05	1.07	1.09	1.01
PARAMETERS									
AUC _{0-t} ($\mu\text{g/mL}\cdot\text{hr}$)	833.86 \pm 133.83		774.27 \pm 129.04		770.59 \pm 127.53		0.93	1.00	1.08
AUC _{inf} ($\mu\text{g/mL}\cdot\text{hr}$)	875.50 \pm 147.51		819.04 \pm 146.52		809.73 \pm 143.81		0.94	1.01	1.08
C _{max} ($\mu\text{g/mL}$)	75.18 \pm 10.62		61.01 \pm 12.95		62.35 \pm 12.55		0.81	0.98	1.21
T _{max} (hr)	2.11 \pm 0.99		3.83 \pm 1.36		3.83 \pm 1.24		1.82	1.00	0.55
t _{1/2}	10.91 \pm 2.09		10.99 \pm 1.92		10.57 \pm 1.68		1.00	1.04	1.03
K _{el} (hr ⁻¹)	0.066 \pm 0.012		0.065 \pm 0.011		0.067 \pm 0.012		0.98	0.97	0.99

TABLE 5 In Vitro Dissolution Testing

Drug (Generic Name): **Diffunisal**
Dose Strength: 250 mg and 500 mg tablets.
ANDA No.: 74-400
Firm: **Danbury Pharmacal, Inc.**
Submission Dates: August 5, 1993.
File Name: **74400SDW.893**

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 0.1M Tris buffer, pH 7.2
Volume: 900 mL
Specifications: NLT (Q) in 30 minutes)
Reference Drug: Dolobid[®] tablets Merck Sharp and Dhome.
Assay Methodology:

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Min)	Test Product Lot # 08654C Strength(mg) 250 mg			Reference Product Lot # T0427 Strength(mg) 250 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
5	62.1		10.2	50.6		27.8
10	93.6		1.6	89.6		7.7
15	98.1		1.7	94.8		4.4
20	99.1		1.4	96.6		2.4
30	100.2		1.3	98.2		2.3
45	100.4		1.4	99.5		2.0
60	100.3		1.7	99.7		1.9

Sampling Times (Min)	Test Product Lot # 08510C Strength(mg) 500 mg			Reference Product Lot # T0849 Strength(mg) 500 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
5	71.6		3.5	26.2		45.9
10	88.9		2.0	78.8		78.8
15	92.9		1.5	92.1		4.3
20	94.2		1.6	95.2		3.1
30	95.2		1.4	97.2		2.7
45	95.6		1.3	98.4		2.4
60	96.0		1.2	98.9		2.0

Table 6

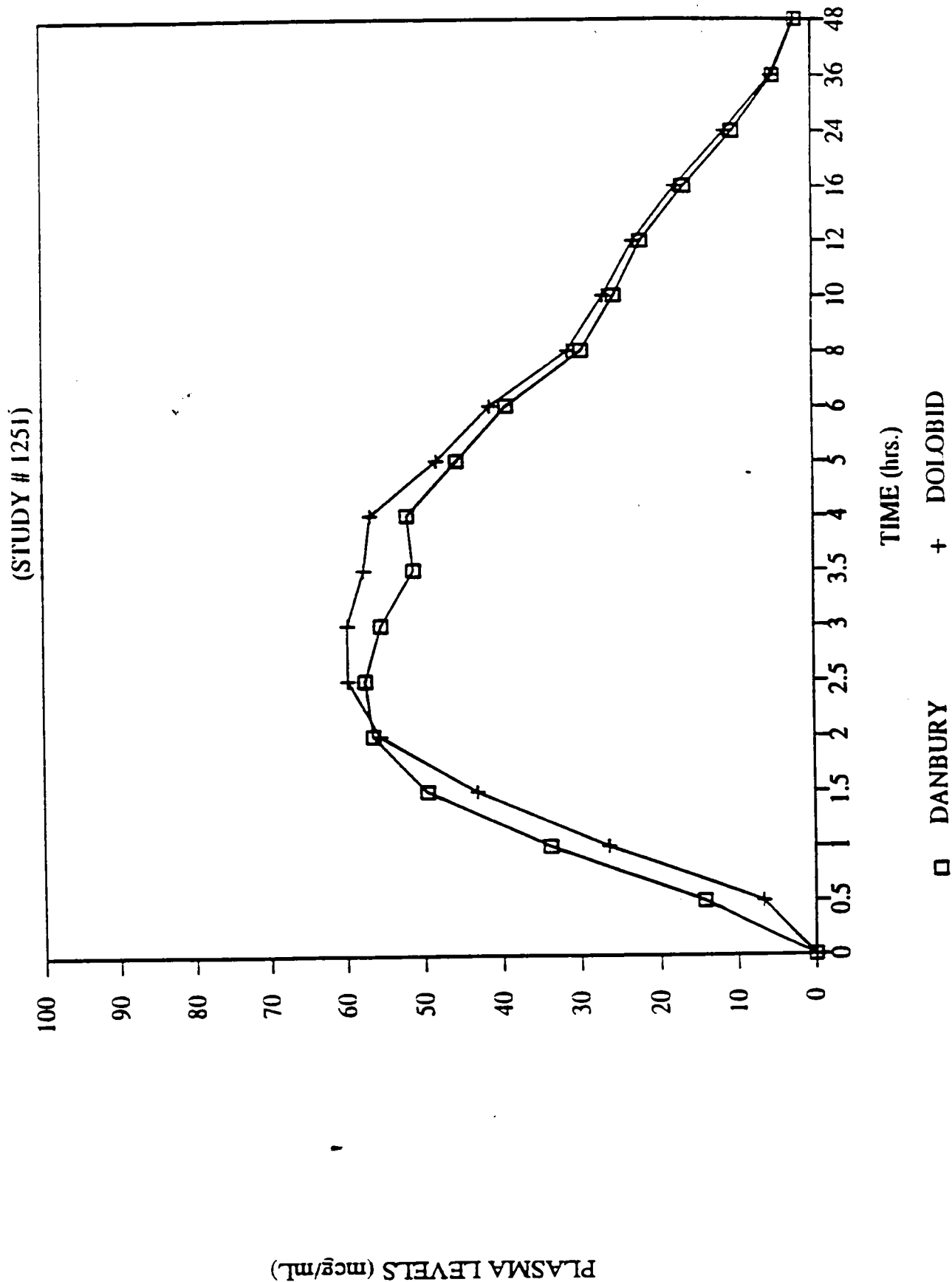
Comparative composition of Danbury Pharmacal's 250 and 500 mg diflunisal tablets (ANDA #74400)

INGREDIENT	MG/TABLET	
	250 mg tablet	500 mg tablet
TABLET CORE		
Diflunisal, USP	250	500
Microcrystalline Cellulose, NF		
Pregelatinized Starch, NF		
Sodium Starch Glycolate, NF		
Starch, NF		
Talc, USP		
Colloidal Silicon Dioxide, NF		
Magnesium Stearate, NF		
Purified Water, USP*	-	-
White *		
Purified Water, USP*		
Total tablet weight	428.4	856.8

* Used in the manufacturing process, but does not appear in the final product (pp 269, vol 1.2).

MEAN PLASMA DIFLUNISAL LEVELS

FIGURE 1



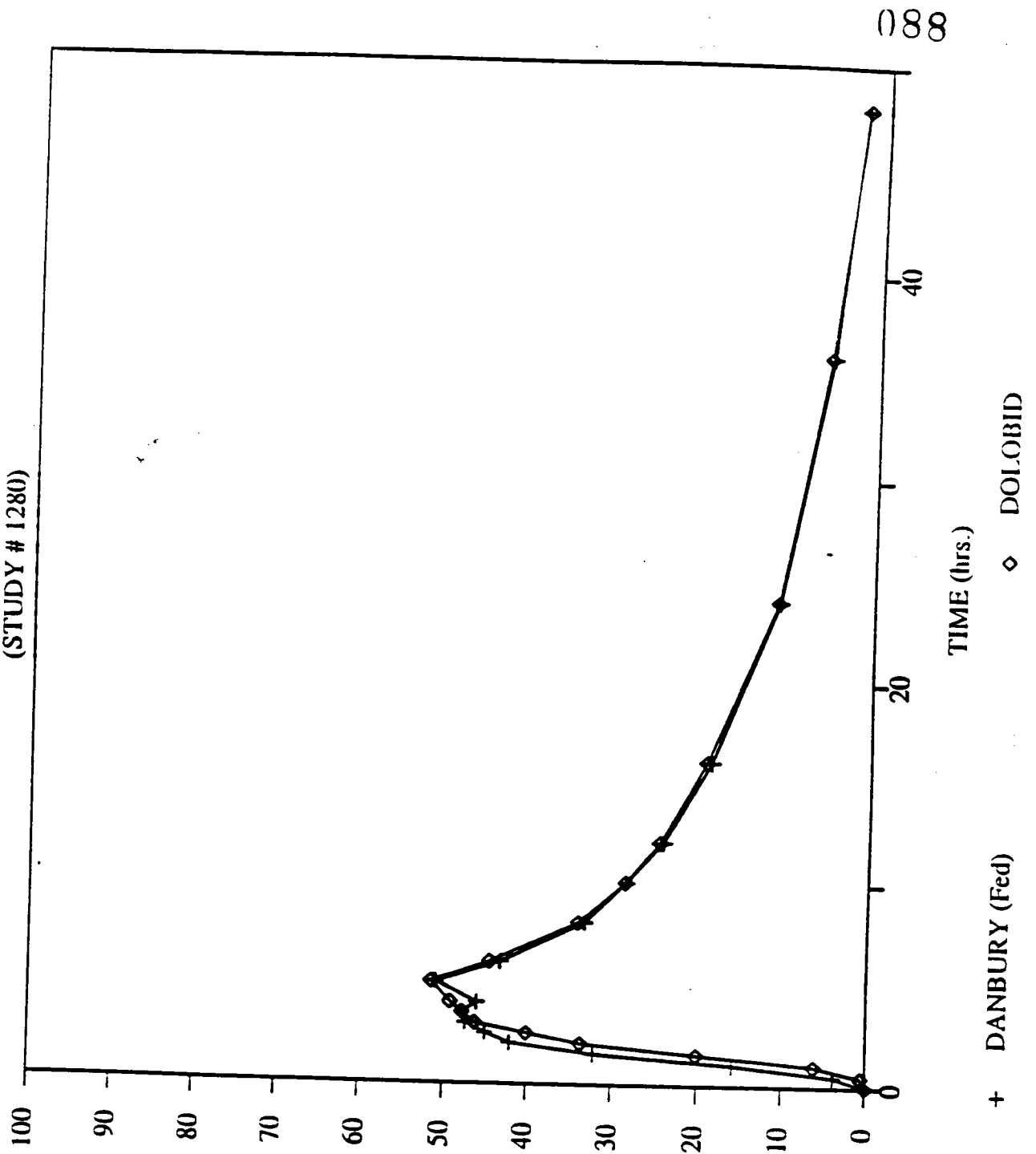
PLASMA LEVELS (mcg/mL)

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FIGURE 2

MEAN PLASMA DIFLUNISAL LEVELS

(STUDY # 1280)



088